Applicants believe that all pending claims are allowable and respectfully request a Notice of Allowance for this application from the Examiner. Should the Examiner believe that a telephone conference would expedite the prosecution of this application, the undersigned can be reached at the telephone number set out below.

Respectfully submitted,
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APPENDIX

**VERSION WITH MARKINGS TO SHOW CHANGES MADE**

12. The method of claim 1, wherein the accessibility correction factor reflects an amphoteric effect manifested by the molecule.

20. The method of claim 19, wherein calculating the parabolic curvature accessibility correction factor comprises:

a) identifying a point on or near one of the atoms in the reactive site;
b) parameterizing at least one parabola using a point on or near an atom that is within about 10[A]Å of the atom in the reactive site; and
outputting a parabolic curvature correction factor.

[26]28. The method of claim 1, wherein the accessibility correction factor reflects hydrophobicity effects at the reactive site of the molecule.

[27]29. The method of claim [26]28, wherein calculating the hydrophobicity effects accessibility correction factor comprises:

a) identifying a reactive atom in the reactive site;
b) identifying atoms connected to the reactive atom;
c) calculating the surface area of at least some of the connected atoms;
d) calculating the partial charge of at least some of the connected atoms;
outputting a hydrophobicity effects correction factor.

[28]30. The method of claim 1, wherein the accessibility correction factor reflects the distance to charged atoms effects at the reactive site of the molecule.

[29]31. The method of claim [28]30, wherein calculating the distance to charged atom effects accessibility correction factor comprises:
a) identifying a reactive atom in the reactive site;
b) calculating the partial charge of atoms on the molecule;
c) identifying a threshold charge;
d) calculating the distance from the reactive atom on the molecule;
e) identifying a threshold distance or threshold degree of connectivity to the reactive atom;
f) outputting a distance to charged atoms effects accessibility correction factor.

# APPENDIX OF PENDING CLAIMS

## CLAIMS

What is claimed is:

1. A method of predicting the susceptibility of a reactive site on a molecule to metabolism, the method comprising:

a) receiving a value of an electronic contribution to reactivity for the site;
b) calculating an accessibility correction factor for the site;
c) applying the accessibility correction factor to the initial activation energy value to generate a new reactivity value for the site; and
d) outputting the new reactivity value for the site.

2. The method of claim 1 wherein (a), (b), (c), and (d) are repeated for multiple reactive sites on the substrate molecule.

3. The method of claim 2, further comprising determining which of the multiple reactive sites is most likely to undergo metabolism.

4. The method of claim 1 wherein the molecule accessibility correction factor is calculated for a cytochrome P450 enzyme.

5. The method of claim 1, wherein the accessibility correction factor reflects how the molecule can orient itself in a metabolic enzyme.

6. The method of claim 1, wherein the accessibility correction factor reflects steric constraints on the accessibility of the site.

7. The method of claim 1, wherein applying the accessibility correction factor to the initial activation energy value comprises summing the accessibility correction factor and the initial activation energy.

8. The method of claim 1, wherein the accessibility correction factor is a function of one or more accessibility descriptors.

9. The method of claim 1, wherein the one or more accessibility descriptors are selected from the group consisting of orientation accessibility descriptors and combinations thereof.

10. The method of claim 1, wherein the one or more accessibility descriptors are selected from the group consisting of steric accessibility descriptors and combinations thereof.

11. The method of claim 1, wherein applying the accessibility correction factor to the initial activation energy value comprises employing the following expression:

$$E_{A\,corr} = E_{A,0} + \sum_{i}^{N\,steric\,descriptors} C_i K_i + \sum_{j}^{M\,orientation\,descriptors} C_j K_j$$

wherein $E_{Acorr}$ is the new reactivity value for the site, wherein $E_{A0}$ is the electronic contribution to reactivity for the site, wherein the $C_i$s and $C_j$s are coefficients for steric and orientation descriptors, respectively, and wherein the $K_i$s and $K_j$s are steric and orientation descriptors.

12. (Amended) The method of claim 1, wherein the accessibility correction factor reflects an amphoteric effect manifested by the molecule.

13. The method of claim 12, wherein the amphoteric effect is calculated by

a) calculating a surface area of each atom on the molecule;
b) calculating a partial charge of each atom on the molecule;
c) calculating an amphoteric moment;
d) extending a vector from a reference point to the reactive site on the molecule;
e) outputting an amphoteric correction factor.

14. The method of claim 1, wherein the accessibility correction factor corrects for a surface area accessibility at the reactive site on the molecule.

15. The method of claim 1, wherein calculating the surface area accessibility correction factor comprises:

a) choosing a probe radius;
b) determining the exposed surface area of an atom in the reactive site;
c) comparing the exposed surface area to a reference value; and
d) outputting a surface area correction factor.

16. The method of claim 15wherein the probe radius is the radius of a solvent molecule.

17. The method of claim 15 wherein the reference value is the surface area of a hydrogen in a methyl group on an aliphatic chain.

18. The method of claim 15 wherein the reference value is the surface area of a carbon in an aromatic group.

19. The method of claim 1, wherein the accessibility correction factor reflects a parabolic curvature effect at the reactive site on the molecule.

20. (Amended) The method of claim 19, wherein calculating the parabolic curvature accessibility correction factor comprises:

a) identifying a point on or near one of the atoms in the reactive site;
b) parameterizing at least one parabola using a point on or near an atom that is within about 10Å of the atom in the reactive site; and
c) outputting a parabolic curvature correction factor.

21. The method of claim 1, wherein the accessibility correction factor reflects protrusion accessibility effects at the reactive site on the molecule.

22. The method of claim 21, wherein calculating the protrusion accessibility correction factor comprises:

a) choosing an atom in the reactive site;
b) extending a vector from a standard point in the molecule to the atom;
c) assigning a score to the vector; and
d) outputting an protrusion accessibility correction factor.

23. The method of claim 1, wherein the accessibility correction factor reflects extension accessibility effects at the reactive site on the molecule.

24. The method of claim 23, wherein calculating the extension accessibility correction factor comprises:

a) choosing an atom in the reactive site;
b) extending a vector from a standard point in the molecule to the atom;
c) assigning a score to the vector; and

d) outputting an extension accessibility correction factor.

25. The method of claim 1, wherein the accessibility correction factor reflects distance to polar regions effects at the reactive site of the molecule.

26. The method of claim 25, wherein calculating the distance to polar regions effects accessibility correction factor comprises:

a) calculating the polarity of each atom on the molecule;
b) identifying at least one range of distances from the reactive site;
c) determining the amount of polarity within each range;
d) outputting a distance to polar regions correction factor for each range.

27. The method of claim 25, wherein the distance to polar regions effects correction factor is weighted by the protrusion of atoms in the range.

28. (Amended) The method of claim 1, wherein the accessibility correction factor reflects hydrophobicity effects at the reactive site of the molecule.

29. (Amended) The method of claim 28, wherein calculating the hydrophobicity effects accessibility correction factor comprises:

a) identifying a reactive atom in the reactive site;
b) identifying atoms connected to the reactive atom;
c) calculating the surface area of at least some of the connected atoms;
d) calculating the partial charge of at least some of the connected atoms;
e) outputting a hydrophobicity effects correction factor.

30. (Amended) The method of claim 1, wherein the accessibility correction factor reflects the distance to charged atoms effects at the reactive site of the molecule.

31. (Amended) The method of claim 30, wherein calculating the distance to charged atom effects accessibility correction factor comprises:

a) identifying a reactive atom in the reactive site;
b) calculating the partial charge of atoms on the molecule;
c) identifying a threshold charge;
d) calculating the distance from the reactive atom on the molecule; identifying a threshold distance or threshold degree of connectivity to the reactive atom; outputting a distance to charged atoms effects accessibility correction factor.

32. A computer-program product comprising a computer-readable medium and program instructions provided via the computer-readable medium, the program instructions comprising instructions for predicting the susceptibility of a reactive site on a molecule to metabolism, the instructions specifying:

a) receiving a value of an electronic contribution to reactivity for the site;
b) calculating an accessibility correction factor for the site;
c) applying the accessibility correction factor to the initial activation energy value to generate a new reactivity value for the site; and
d) outputting the new reactivity value for the site.

33. The computer-program product of claim 32, further comprising instructions for repeating (a) through (d) for multiple reaction sites on the molecule.

34. The computer-program product of claim 32 wherein the molecule accessibility correction factor is calculated for a cytochrome P450 enzyme.

35. The computer-program product of claim 32, wherein the accessibility correction factor reflects how the molecule can orient itself in a metabolic enzyme.

36. The computer-program product of claim 32, wherein the accessibility correction factor reflects steric constraints on the accessibility of the site.

37. The computer-program product of claim 32, wherein the accessibility correction factor is a function of one or more accessibility descriptors.

38. The computer-program product of claim 32, wherein the one or more accessibility descriptors are selected from the group consisting of orientation accessibility descriptors, steric accessibility descriptors, and combinations thereof.

39. The computer-program product of claim 32, wherein instructions specifying applying the accessibility correction factor to the initial activation energy value comprise employing the following expression:

$$E_{A\,corr} = E_{A,0} + \sum_{i}^{N\,steric\,descriptors} C_i K_i + \sum_{j}^{M\ orientation\ descriptors} C_j K_j$$

wherein $E_{Acorr}$ is the new reactivity value for the site, wherein $E_{A0}$ is the electronic contribution to reactivity for the site, wherein the $C_i$s and $C_j$s are coefficients for steric and orientation descriptors, respectively, and wherein the $K_i$s and $K_j$s are steric and orientation descriptors.

40. The computer-program product of claim 32, wherein the accessibility correction factor reflects an amphoteric effect manifested by the molecule.

41. The computer-program product of claim 40, wherein the amphoteric effect is calculated by

a) calculating a surface area of each atom on the molecule;
b) calculating a partial charge of each atom on the molecule;
c) calculating an amphoteric moment;
d) extending a vector from a reference point to the reactive site on the molecule;
e) outputting an amphoteric correction factor.

42. The computer-program product of claim 32, wherein the accessibility correction factor corrects for a surface area accessibility at the reactive site on the molecule.

43. The computer-program product of claim 42, wherein calculating the surface area accessibility correction factor comprises:

a) choosing a probe radius;
b) determining the exposed surface area of an atom in the reactive site;
c) comparing the exposed surface area to a reference value; and
d) outputting a surface area correction factor.

44. The computer-program product of claim 43 wherein the probe radius is the radius of a solvent molecule.

45. The computer-program product of claim 32, wherein the accessibility correction factor reflects a parabolic curvature effect at the reactive site on the molecule.

46. The computer-program product of claim 45, wherein calculating the parabolic curvature accessibility correction factor comprises:

a) identifying a point on or near one of the atoms in the reactive site;
b) parameterizing at least one parabola using a point on or near an atom that is within about 10Å of the atom in the reactive site; and

c) outputting a parabolic curvature correction factor.

47. The computer-program product of claim 32, wherein the accessibility correction factor reflects protrusion accessibility effects at the reactive site on the molecule.

48. The method of claim 47, wherein calculating the protrusion accessibility correction factor comprises:

a) choosing an atom in the reactive site;
b) extending a vector from a standard point in the molecule to the atom;
c) assigning a score to the vector; and
d) outputting an protrusion accessibility correction factor.

49. The computer-program product of claim 32, wherein the accessibility correction factor reflects extension accessibility effects at the reactive site on the molecule.

50. The computer-program product of claim 49, wherein calculating the extension accessibility correction factor comprises:

a) choosing an atom in the reactive site;
b) extending a vector from a standard point in the molecule to the atom;
c) assigning a score to the vector; and
d) outputting an extension accessibility correction factor.

51. The computer-program product of claim 32, wherein the accessibility correction factor reflects distance to polar regions effects at the reactive site of the molecule.

52. The computer-program product of claim 51, wherein calculating the distance to polar regions effects accessibility correction factor comprises:

a) calculating the polarity of each atom on the molecule;
b) identifying at least one range of distances from the reactive site;
c) determining the amount of polarity within each range;
d) outputting a distance to polar regions correction factor for each range.

53. The computer-program product of claim 51, wherein the distance to polar regions effects correction factor is weighted by the protrusion of atoms in the range.

54. The computer-program product of claim 32, wherein the accessibility correction factor reflects hydrophobicity effects at the reactive site of the molecule.

55. The computer-program product of claim 54, wherein calculating the hydrophobicity effects accessibility correction factor comprises:

a) identifying a reactive atom in the reactive site;
b) identifying atoms connected to the reactive atom;
c) calculating the surface area of at least some of the connected atoms;
d) calculating the partial charge of at least some of the connected atoms;
e) outputting a hydrophobicity effects correction factor.

56. The computer-program product of claim 32, wherein the accessibility correction factor reflects the distance to charged atoms effects at the reactive site of the molecule.

57. The computer-program product of claim 56, wherein calculating the distance to charged atom effects accessibility correction factor comprises:

a) identifying a reactive atom in the reactive site;
b) calculating the partial charge of atoms on the molecule;
c) identifying a threshold charge;
d) calculating the distance from the reactive atom on the molecule;
e) identifying a threshold distance or threshold degree of connectivity to the reactive atom; outputting a distance to charged atoms effects accessibility correction factor

58. A method of producing a model that predicts the lability of reactive sites on a chemical compound, the method comprising:

a) obtaining structural representations for a training set of chemical compounds;
b) for each of said chemical compounds, identifying one or more reactive sites pertinent to the model;
c) for each of said reactive sites,
(i) determining whether metabolism is experimentally observed or predicted; and
(ii) characterizing the reactive site in terms of values for a plurality of chemical descriptors wherein the descriptors are chosen to represent structural features reflecting at least one of steric and orientation effects in impacting access of the compounds to the binding site of a metabolizing enzyme; and
d) for all of said reactive sites, using the site of metabolism information and chemical descriptor values to obtain an expression for lability.

59. The method of claim 58, wherein the structural representations are three dimensional depictions including at least bond lengths and bond angles.

60. The method of claim 58, wherein identifying reactive sites pertinent to the model comprises identifying sites where the oxidation reaction can occur on the chemical compounds of the training set.

61. The method of claim 58, wherein the one or more chemical descriptors further comprise descriptors characterizing the electronic reactivity of the training set compounds.

62. The method of claim 58, wherein using the site of metabolism information and the chemical descriptor values to obtain an expression for lability comprises employing a data fitting technique.

63. The method of claim 62, wherein the data fitting technique is selected from the group consisting of partial least squares, principal component analysis, back-propagation neural networks and genetic algorithms.

64. The method of claim 58, wherein using the site of metabolism information and the chemical descriptor values to obtain an expression for lability comprises calculating a linear expression equation, each descriptor having a coefficient, the method comprising employing a regression technique to calculate the coefficients and the regression equation.

65. The method of claim 58, wherein the method further comprises deriving a confidence score for the calculating the relative atom stability of each reactive site and deriving a confidence score for the results predicted by the model, the method comprising:

a) using the expression to obtain predictions of lability for the reactive sites of a set of molecules;
b) calculating the relative atom stability for each reactive site; and
c) deriving a confidence score from the relative atom stabilities of the reactive sites.